

REMARKS

Claims 45-79, presented hereby, are pending.

Claims 32-44 are cancelled hereby, without prejudice or disclaimer.

Present method claim 45 corresponds to independent claim 32 limited to the method of treating "radiomucositis," i.e., deleting the phrase "or of chemomucositis" from line 1 of the claim.

Present claim 46 corresponds to claim 33 amended to depend on present claim 45.

Present method claim 47 corresponds to independent claim 34.

Present composition claim 48 corresponds to independent claim 35 amended by deleting "or of chemomucositis induced by radiotherapy or combined radiochemotherapy" from lines 1-2 of the claim. Present composition claims 49-57 correspond to claims 36-44 amended to be dependent, directly or indirectly, on present claim 48.

Present composition claim 58 corresponds to claim 35 amended as in present claim 48, and, further amended, by limiting the recited "effective quantity of a compound chosen from flavanoids and isoflavonoids" (in claim 35) to "0.5 to 10% of a rutoside," such as described in working example 7 of the subject application (*see* table on page 12). Composition claims 59 and 60, which are dependent on present claim 58, contain subject matter found in working examples 5 and 6 of the subject application (*see* table at page 12). Present composition claims 61-69, which are directly or indirectly dependent on present claim 58, contain subject matter found in claims 36-44, respectively.

Present method claim 70 combines subject matter of claim 32 and claim 58, and present claim 71 depends on claim 70.

Present composition claims 72-79 use the transitional phrase "*consisting of*" and, thereby, exclude any non-recited components.

The method claims, except for claims 70 and 71, are limited to treatment of radiomucositis (by radiotherapy or combined radiochemotherapy). Treating chemomucositis is recited in method claims 70 and 71, only.

The composition claims no longer recite chemomucositis.

Claims 32-44 were rejected under 35 USC 103(a) as being allegedly unpatentable over US 4,748,022 (Busciglio) in view of US 6,333,044 (Santus). Reconsideration is requested.

Busciglio discloses a composition and method for the treatment of ulcers on mucosal surfaces (in fact, oral lesions). The composition, which can be a gel, comprises several active agents, namely diphenylamine, lidocain, aloe, and propolis, and a base. Propolis is known to contain a flavonoid, which is present in a bee propolis, having potential applications. B Havesteen, *Biochemical Pharmacology*, 32, 1141-1148, 1983 (copy attached).

Among various disclosed lesions there is found ulcers caused by chemotherapy.

First, there is no teaching or suggestion in Busciglio to use its composition in connection with mucositis resulting from or associated with radiotherapy.

Radiotherapy exerts very specific highly damaging and destructive effects on tissues and cells in a relatively short time. Further, radiotherapy is known for its potential risk of modifying organic compounds. X-rays or γ rays are used, for example, to sterilize preparations and to cure (cross-link) reagents, and their activity is relatively unpredictable.

Thus, it could not have been obvious for one skilled in the art to use the compound/vehicle mixture according to the presently claimed method for treatment of radiomucositis or mucositis caused by combined radiochemotherapy. There would also have been no teaching or suggestion for the presently claimed composition useful for the treatment of radiomucositis, especially as defined in claims 72-79.

Present claims 72-79 are limited to a composition "consisting of" only a single flavonoid or isoflavanoid. Busciglio uses propolis, which contains several naturally occurring flavonoids where, in the present invention, the flavonoid is precisely identified pure flavonoid.

Busciglio teaches a very specific formulation having five critical ingredients, namely diphenyldramine, lidocain, aloe, propolis, and a base. There is no motivation in the cited art for eliminating one, let alone four, of the critical ingredients. Thus, the fact that Busciglio discusses a possible, previously unknown effect of his combined ingredients is not an incentive to select only one of the ingredients.

Busciglio considers that there is a cooperation among all his ingredients necessary to secure the positive effect observed. Busciglio's aim is to provide relatively long-lasting relief of symptoms associated with oral-cavity lesions (column 2, lines 49-54) and promote healing of the lesions. There is no suggestion about the improvement secured by the presently claimed invention in the field of radiotherapy, which allows prevention and immediate repair of lesions produced during radiotherapy treatment. When used for such treatment, a composition will be subjected to radiotherapy irradiation. There was no teaching or suggestion that either the gel composition or the flavanoid or isoflavanoid, as active ingredient, would remain stable and efficient under such conditions.

Flavonoids, such as rutine, under such conditions are potent anti-oxidants and free radical scavengers. It was discovered that, under irradiation, rutine keeps its potent effects. Moreover, the antiradical efficiency of the formulation according to the presently claimed invention has been tested by the so-called Rancimat test, which determines the stability of fat compositions against oxidation by measuring the quantity of organic acids freely released during irradiation at 20 Gray. A free release during irradiation at 20 Gray shows no degradation of the gel or of the active agent. Rutine remains rapidly absorbed by producing quercetine and rutinose, and the assay shows that absorption of the rutine by the mucosa was very fast; after 24 h, 65.5% of the hydrosoluble rutine is present in the mucosa. This evidence shows that the present claims are not obvious under §103(a).

With regards to the present claims limited to quantitative features, Busciglio teaches that the amount of propolis can be from 1 to 2% of the total formulation. Propolis contains far more than flavonoids, alone. Propolis is an organic mixture, i.e., a plant juice honey and resin. Bees make the resinous propolis from fluids gathered from plants (see Havesteen, *supra*, page 1142, left column, last paragraph). No content of flavonoid is given, but it is *prima facie* clear that flavonoids can constitute only a small part of propolis. Thus, there is no suggestion of the amounts recited in the present claims, especially the amount "0.5 to 10%" as recited in present claim 58.

The secondary reference, Santus, provides neither teaching nor suggestion for curing the fatal deficiencies in Busciglio, as explained above.

Santus teaches compositions with analgesic and anti-inflammatory activity, which include Keterolac or its salts, for administration by the intra nasal route. Keterolac is thereby rapidly and

thoroughly absorbed, giving a therapeutic effect equivalent to that obtained by intravenous or intramuscular administration (column 2, lines 15-20).

The Santus composition is taught to be particularly effective in acute therapies, where very rapid systemic delivery is required (column 2, lines 33-37). It compares favorably with intravenous formulations in terms of absorption (systematic distribution) (see column 10, last paragraph). In other words, the Santus vehicle is aimed to very rapidly deliver active ingredients for a systemic distribution far from the location of administration.

On the contrary, the treatment of mucositis according to the present claims is a specifically local treatment, where the active agent has to be administered near irradiated tissues to be delivered to these tissues, and active, during radiotherapy.

Santus also teaches that there are very few therapeutic agents that are able to be administrated by the intra nasal route, which is mucosal (see column 2, line 43-49). Thus, combining Busciglio with Santus by distributing the Busciglio formulation in the Santus vehicle would not have been obvious because, obviously, the Santus formulation is intended for rapid absorportion. Even effecting such a combination would not lead to the presently claimed method or composition. As discussed above, propolis is only one of the five critical ingredients of Busciglio, and Santus gives no incentive to select only flavonoids. Further, neither cited reference provides any suggestion that the presently claimed composition would be of any use for treating mucositis associated with radiotherapy and, even less, for being efficient and retaining its properties during radiotherapy.

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Favorable action is requested.

Respectfully submitted,

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